give colorless needles of **9**, mp 73–74°, nmr consistent. *Anal.* ($C_4H_6Cl_3NS$) C, H, N, S.

2,2-Dimethylthiazolidine Hydrochloride (**10**).—Thiol 1 (16.84 g, 148 mmoles) was dissolved in MeOH (25 ml) and excess Me_2CO (300 ml), and the mixture was heated under reflux for 8.5 hr. Evaporation of solvent gave a residue (20.3 g), mp 162–166°, which was crystallized three times from MeOH by addition of Et_2O to give **10** as colorless needles (8.6 g, 38%), having constant mp 170–171.5° (lit.[3d] 164–165°). *Anal.* ($C_5H_{12}ClNS$) C, H, S.

2-Benzoylthiazolidine Hydrochloride (**11**).—Thiol 1 (5.50 g, 48.5 mmoles) and phenylglyoxal hydrate (7.60 g, 50 mmoles) were heated together at *ca.* 85° for *ca.* 5 min; the mixture then was dissolved in MeOH (30 ml) and Et_2O (120 ml) was added to incipient turbidity. Cooling gave colorless **11** (4.4 g, 39%), mp 151–153° dec. Recrystallization three times from MeOH by addition of Et_2O gave **11** with a melting point of 151.5–152.5° dec, nmr consistent. *Anal.* ($C_{10}H_{12}ClNOS$) C, H, N, S.

Spiro[2,3-dihydroindole-3,2′-thiazolidine]-2-one Hydrochloride (**12**).—Finely powdered isatin (10.95 g, 75 mmoles) was slowly added to thiol 1 (8.5 g, 75 mmoles) in *i*-PrOH (80 ml) to give a red mixture which, after being stirred for 24 hr at *ca.* 25°, became pale brown. Filtration separated pale brown **12** (15.4 g, 85%), mp 200–203° dec. A sample was recrystallized three times from MeOH by addition of Et_2O and had a constant melting point of 203–204° dec; ir (KBr), 2370, 1735 (amide C=O) cm^{-1}. *Anal.* ($C_{10}H_{11}ClN_2OS$) C, H, N, S.

D-5,5-Dimethylthiazolidine-4-carboxylic Acid (**13**).—D-Penicillamine (35 g, 235 mmoles)[10] was dissolved in 45% aqueous HCHO (200 ml, 3.0 moles). Within *ca.* 5 min, solid started to separate. The mixture was stirred for *ca.* 20 hr. Filtration then removed the colorless intermediate **14** (29 g, 69%), mp 111–112°, after a wash with dioxane then Et_2O and drying over silica gel; ir (KBr), 3420, 2990, 2750, 1635, 1475, 1400, 1380, 1360, 1340, 1135 (s), 1105, 1010, 830, and 705 cm^{-1}. Conversion to the thiazolidine **13**, generally in *ca.* 75% yields, was achieved by dissolving the intermediate **14** in H_2O (10 ml/g of **14**) and adding EtOH (4 vol) to incipient turbidity, then cooling. The thiazolidine **13** had mp 195–195.5° dec,[11] ir and nmr consistent.

(10) Kindly supplied by Dr. Elmer Alpert, Merck Sharp and Dohme Research Laboratories, West Point, Pa.

(11) Reference 4, p 958, reports mp 196–197° dec. The melting point reported there for the L form was 193–194°; a later patent abstract indicates this preparation was from L-penicillamine rather than the hydrochloride, but the identity of the procedures suggests an error in the abstract [J. H. Hunter and B. E. Leach, U. S. Patent 2,480,079 (1949); *Chem. Abstr.*, **44**, 2569 (1950)].

Quaternary Thiazolylpyridinium Salts. Oral Hypoglycemic Agents

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A series of quaternary 4-(thiazolyl)pyridinium salts has been synthesized. Blood glucose concentration of normal mice was decreased following oral administration of these compounds.

A number of azolylpyridinium salts, including members of the pyrazolyl-,[1] isoxazolyl-,[2-4] 1,2,4-oxadiazolyl-,[5] and oxazolylpyridinium[6] salt families, have been found to induce hypoglycemia in laboratory animals. As a further development of this series, we have investigated the replacement of the five-membered ring with still other heterocycles. We describe herein the synthesis of some novel 4-(thiazolyl)pyridinium salts. The choice of substituents was influenced by structure–activity correlations developed in the pyrazolylpyridinium salt series.[1]

The 4-(thiazolyl)pyridinium salts **10–29** were prepared from the thiazolylpyridine bases **4–9** by quaternization with the appropriate alkyl halide. The base **4** was prepared as described by Wallenfels and Gellrich.[7] The bases **5**, **7**, and **8** were prepared by modification of this procedure. Thus, reaction of thioisonicotinamide with 3-bromo-2-butanone gave **5**, reaction of thioacetamide with **1**[8] gave **7**, and reaction of cyclopropanethiocarboxamide with **1** gave **8**. The bases **6** and **9** were prepared by fusion of the amido ketones **2**[5] and **3**,[9] respectively, with P_2S_5 using a modification of the procedure of Gabriel[10] as described by Ott, *et al.*,[11] for the preparation of arylthiazoles.

In the nmr spectra of the 4-(thiazolyl)pyridine bases **4–9**, the pyridyl protons appear as two doublets at δ 7.73–7.76 and 8.60–9.01. Upon quaternization, these signals shift to new values of δ 8.33–8.53 and 8.83–9.18. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, were found to be diagnostic of pyridine quaternization in our earlier study of pyrazolylpyridinium salts.[1,12] Spin-decoupling experiments demonstrate that the quaternary methyl of **11** is coupled with the α-pyridyl protons, further confirming that alkylation has occurred on the pyridyl nitrogen.

Hypoglycemic Activity.[13]—Saline solutions or 0.5% aqueous carboxymethylcellulose suspensions of test compounds were administered by gavage to male CF-1 mice (Carworth Farms, 25–30 g) at doses of 0.5–1.5 mmol/kg; controls received an equal volume of vehicle.

(1) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, **11**, 981 (1968).

(2) V. J. Bauer, W. J. Fanshawe, H. P. Dalalian, and S. R. Safir, *ibid.*, **11**, 984 (1968).

(3) D. A. Blickens and S. J. Riggi, *Toxicol. Appl. Pharmacol.*, **14**, 393 (1969); *Diabetes*, in press.

(4) S. J. Riggi, D. A. Blickens, and C. R. Boshart, *ibid.*, **17**, 646 (1968).

(5) W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *J. Med. Chem.*, **12**, 381 (1969).

(6) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 943 (1969).

(7) K. Wallenfels and M. Gellrich, *Ann. Chem.*, **621**, 210 (1959).

(8) L. Polo-Friz, *Farmaco, Ed. Sci.*, **18**, 972 (1963).

(9) S. van der Meer, H. Kofmann, and H. Veldstra, *Rec. Trav. Chim. Pays-Bas*, **72**, 236 (1953).

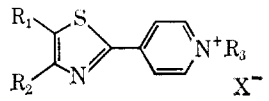
(10) S. Gabriel, *Chem. Ber.*, **43**, 134 (1910).

(11) D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Amer. Chem. Soc.*, **78**, 1941 (1956).

(12) V. J. Bauer, H. P. Dalalian, and S. R. Safir, *J. Med. Chem.*, **11**, 1263 (1968).

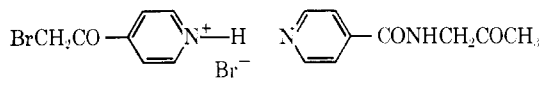
(13) Technical assistance of Mr. E. Locke, Mr. H. Siegriest, and Miss L. Will is greatly appreciated.

TABLE I
4-(2-THIAZOLYL)PYRIDINIUM SALTS



Compd	R_1	R_2	R_3	X	Mp, °C dec	Recrystn solvent	Formula	Analyses	% decrease in blood glucose[a] 0.5 mmol/kg	1.5 mmol/kg	Control
10	H	CH_3	CH_3	I	218	*i*-PrOH–H_2O	$C_{10}H_{11}IN_2S$	C, H, I, N	33 ± 18[b]	61 ± 19[c]	9 ± 8
11	H	CH_3	CH_3	Cl	243–244	MeCN	$C_{10}H_{11}ClN_2S$	C, H, Cl, N, S	33 ± 3[b]	90 ± 2[c]	1 ± 4
12	H	CH_3	C_2H_5	Br	197–199	MeCN	$C_{11}H_{13}BrN_2S$	C, H, Br, N, S	30 ± 4	84 ± 2	12 ± 5
13	H	CH_3	*n*-C_3H_7	Br	199–201	MeCN	$C_{12}H_{15}BrN_2S$	C, H, N, S; Br[d]	28 ± 5	65 ± 7	1 ± 3
14	H	CH_3	CH_2=$CHCH_2$	Cl	188–189	MeCN	$C_{12}H_{13}ClN_2S$	C, H, Cl, N, S	64 ± 12	60 ± 18	31 ± 7
15	H	CH_3	CH_2=$CHCH_2$	Br	200–201	MeCN	$C_{12}H_{13}BrN_2S$	C, H, Br, N, S			
16	H	CH_3		Br	223–224	MeCN	$C_{13}H_{15}BrN_2S$	C, H, Br, N, S	24 ± 3	49 ± 16	1 ± 3
17	H	CH_3	$C_2H_5OC_2H_4$	Cl	89–92	Me_2CO	$C_{13}H_{17}ClN_2OS \cdot 0.5H_2O$	C, H, N, S; Cl[e]	46 ± 7	84 ± 5	1 ± 3
18	CH_3	H	CH_3	I	238–239	EtOH–Et_2O	$C_{10}H_{11}IN_2S$	C, H, I, N, S	56 ± 15	82 ± 5	15 ± 7
19	CH_3	CH_3	CH_3	Cl	225–226	MeCN–Et_2O	$C_{11}H_{13}ClN_2S \cdot 0.25H_2O$	C, H, N, S; Cl[f]	51 ± 8	64 ± 7	4 ± 6

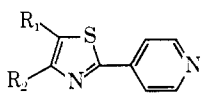
[a] Values are means ± standard errors of four to six mice. Maximal reductions in blood glucose concentrations 3 or 5 hr after dosing are expressed as per cent decrease from predose values. Control animals were dosed orally with vehicle. Average predose blood glucose concentration for 74 control mice was 123 ± 2 mg/100 ml. [b] 0.4 mmol/kg. [c] 0.8 mmol/kg. [d] Br: calcd, 26.7; found, 27.2. [e] Cl: calcd, 12.1; found, 12.8. [f] Cl: calcd, 14.5; found, 15.2.



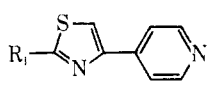
1

2

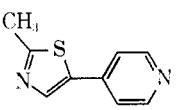
3



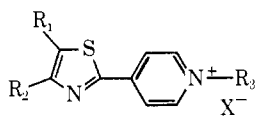
4, $R_1 = H$; $R_2 = CH_3$
5, R_1; $R_2 = CH_3$
6, $R_1 = CH_3$; $R_2 = H$



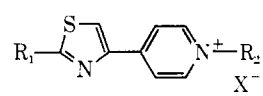
7, $R_1 = CH_3$
8, $R_1 =$



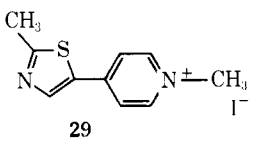
9



10–19 (Table I)



20–28 (Table II)



29

Blood samples (0.05 ml) obtained from retrobulbar plexuses 3 and 5 hr after dosing were assayed[4] for blood glucose using the method of Hoffman[14] as adapted for the Technicon AutoAnalyzer. Results are included in Tables I and II. Blood glucose concentration was significantly reduced following administration of the 4-(thiazolyl)pyridinium salts. The average decreases from control of 37 ± 4 (**20–28**) and 63 ± 7% (**10–19**) at a dose of 1.5 mmol/kg suggest that the 4-(4-thiazolyl)pyridinium salts are less active than the 4-(2-thiazolyl)pyridinium compounds.

(14) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

Experimental Section[15]

4-(4,5-Dimethyl-2-thiazolyl)pyridine (5).—A mixture of 5 g (0.036 mol) of thioisonicotinamide, 8.8 g (0.058 mol) of 3-bromo-2-butanone, and 50 ml of EtOH was heated under reflux for 6 hr and concentrated under reduced pressure to dryness. A suspension of the solid residue in 50 ml of H_2O was made alkaline (1 *N* NaOH) and extracted ($CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure to a solid residue which was sublimed at 80° (0.05 mm) to give 1.9 g (30%) of off-white crystals. Recrystallization (EtOH–H_2O) gave colorless crystals: mp 101–102°; uv, 318 mμ (ε 15,410); nmr (DMSO-d_6), δ 2.35 and 2.41 (s, 3 each, CH_3), 7.76 and 9.01 (d, J = 6 cps, 2 each, pyridyl-H). *Anal.* ($C_{10}H_{10}N_2S$) C, H, N, S.

4-(5-Methyl-2-thiazolyl)pyridine (6).—A mixture of 2 g (0.011 mol) of isonicotinamidoacetone (**2**)[6] and 3 g (0.013 mol) of P_2S_5 was heated at 110–140° until gas evolution ceased. The oily residue was warmed with excess 1 *N* KOH and extracted ($CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure to 1.5 g (80%) of tan crystals. Sublimation at 65° (0.05 mm) gave yellow needles: mp 88–90°. *Anal.* ($C_9H_8N_2S$) C, H, N.

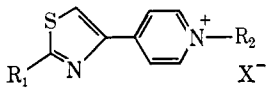
4-(2-Methyl-4-thiazolyl)pyridine (7).—A mixture of 18.2 g (0.27 mol) of thioacetamide, 37.8 g (0.135 mol) of 4-bromoacetylpyridine hydrobromide (**1**),[8] and 1 l. of MeOH was heated under reflux for 0.5 hr and concentrated under reduced pressure. A solution of the solid residue in 100 ml of H_2O was made alkaline (1 *N* NaOH) and extracted ($CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure to a yellow solid. Recrystallization (C_6H_6–cyclohexane) gave 20 g (84%) of tan crystals, mp 79–80°. *Anal.* ($C_9H_8N_2S$) C, H, N, S.

4-(2-Cyclopropyl-4-thiazolyl)pyridine (8), prepared from cyclopropanethiocarboxamide and 4-bromoacetylpyridine hydrobromide (**1**)[8] using the method described above for the synthesis of **7**, was obtained as a colorless oil by evaporative distillation at 100° (0.1 mm), and was converted to the quaternary salt **28** (Table II) without further purification.

4-(2-Methyl-5-thiazolyl)pyridine (9).—A mixture of 1.5 g (0.084 mol) of 4-acetylaminoacetylpyridine (**3**)[9] and 2.3 g (0.104 mol) of P_2S_5 was heated at 110–140° until the evolution of H_2S ceased. The solid mass was heated with excess 1 *N* KOH and the mixture was extracted ($CHCl_3$). The $CHCl_3$ solution was

(15) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Uv spectra were determined in MeOH solution with a Cary 11 spectrophotometer, ir spectra were recorded on KBr disks with a Perkin-Elmer Model 21 infrared spectrophotometer, and nmr spectra were determined with a Varian Associates A-60 spectrometer with TMS or DSS as an internal standard by Mr. W. Fulmor and staff.

TABLE II
4-(4-THIAZOLYL)PYRIDINIUM SALTS



Compd	R_1	R_2	X	Mp, °C dec	Recrystn solvent	Formula	Analyses	% decrease in blood glucose[a] 1.0 mmol/kg	1.5 mmol/kg	Control
20	CH_3	CH_3	Cl	228–231	EtOH–Et_2O	$C_{10}H_{11}ClN_2S$	C, H, Cl, N, S	30 ± 11[b]	64 ± 12[c]	9 ± 4
21	CH_3	C_2H_5	Br	201–202	MeCN	$C_{11}H_{13}BrN_2S$	C, H, Br, N, S	23 ± 6	37 ± 8	9 ± 3
22	CH_3	n-C_3H_7	Br	121–123	Me_2CO	$C_{12}H_{15}BrN_2S \cdot 0.25H_2O$	C, H, Br, N, S	39 ± 7	32 ± 5	4 ± 8
23	CH_3	$CH_2{=}CHCH_2$	Cl	165–167	MeCN	$C_{12}H_{13}ClN_2S$	C, H, Cl, N, S	37 ± 9	37 ± 14	2 ± 8
24	CH_3	$CH_2{=}\overset{\displaystyle CH_3}{\overset{\vert}{C}}CH_2$	Cl	185–186	MeCN	$C_{13}H_{15}ClN_2S$	C, H, Cl, N, S	18 ± 9	31 ± 5	−6 ± 4
25	CH_3	$C_6H_5CH{=}CHCH_2$	Cl	144–146	Me_2CO–MeCN	$C_{18}H_{17}ClN_2S \cdot 0.5H_2O$	C, H, Cl, N, S	46 ± 2	36 ± 6	4 ± 8
26	CH_3		Br	189–191	EtOH–Et_2O	$C_{13}H_{15}BrN_2S$	C, H, Br, N, S	30 ± 6	34 ± 5	9 ± 3
27	CH_3	$C_2H_5OC_2H_4$	Cl	79–80	Me_2CO	$C_{13}H_{17}ClN_2OS$	C, H, Cl, N, S	41 ± 13	50 ± 10	−5 ± 5
28		CH_3	I	233–234	MeCN	$C_{12}H_{13}IN_2S$	C, H, I, N, S	64 ± 18		13 ± 6

[a] Values are means ± standard errors of four to six mice. Maximal reductions in blood glucose concentrations 3 or 5 hr after dosing are expressed as per cent decrease from predose values. Control animals were dosed orally with vehicle. An increase in blood glucose is indicated by a negative sign (−). Average predose blood glucose concentration for 74 control mice was 123 ± 2 mg/100 ml. [b] 0.8 mmol/kg. [c] 1.6 mmol/kg.

dried ($MgSO_4$) and concentrated under reduced pressure to 1.2 g (81%) of pale yellow crystals. Sublimation at 65° (0.05 mm) gave hygroscopic colorless needles: mp <30°. *Anal.* ($C_9H_8N_2S$) C, N, S; H: calcd, 4.58; found, 5.04.

1-Methyl-4-(4-methyl-2-thiazolyl)pyridinium Chloride (11).—A mixture of 10.5 g (0.06 mol) of 4-(4-methyl-2-thiazolyl)pyridine (**4**)[7] and 10 ml of MeCl was heated at 120° for 18 hr in a glass-lined steel bomb. The excess MeCl was allowed to evaporate and the residue was recrystallized (MeCN) to give 10.2 g (75%) of yellow crystals: mp 242–244° dec; ir (KBr), 6.10 μ; uv, 348 mμ (ϵ 17,460), 245 (6580); nmr (D_2O), δ 2.58 (d, J = 1 cps, 3, CCH_3), 4.48 (s, 3, NCH_3), 7.64 (d, J = 1 cps, 1, thiazolyl-H), 8.41 and 8.87 (d, J = 7 cps, 2 each, pyridyl-H). *Anal.* ($C_{10}H_{11}ClN_2S$) C, H, Cl, N, S.

1-Methyl-4-(2-methyl-5-thiazolyl)pyridinium Iodide (29).—A mixture of 1.8 g (0.10 mol) of **9**, 5 ml of MeI, and 30 ml of EtOH was heated under reflux for 1 hr and concentrated under reduced pressure to dryness. The solid residue was recrystallized (MeCN–Et_2O) to give 2.0 g (62%) of yellow crystals, mp 253–255° dec. *Anal.* ($C_{10}H_{11}IN_2S$) C, H, N.

Blood glucose concentration of mice 5 hr after oral administration of 1.0 or 1.5 mmol/kg of **29** was decreased 33 ± 5 and 26 ± 6%, respectively; an increase of 4 ± 5% occurred in saline control mice.

4-(Thiazolyl)pyridinium salts 10–28 were prepared by reaction of the requisite thiazolylpyridine **4–9** with an alkyl halide either in a bomb at 100–120° for 4–18 hr without solvent (as for **11**, above) or in EtOH (as for **29**, above) under reflux. Properties are listed in Tables I and II.